ANNUAL REPORT

OF

THE HOWE LABORATORY

OF

OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

AT THE

MASSACHUSETTS EYE AND EAR
INFIRMARY

1971

243 CHARLES STREET
BOSTON, MASSACHUSETTS 02114

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HOWE LABORATORY OF OPHTHALMOLOGY
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Herewith is the Annual Report of the Howe Laboratory for 1971. It represents the conscientious endeavors of dedicated investigators to learn as much as possible about the visual system and its afflictive disorders. It also represents the generosity and thoughtfulness of a large number of others who have supported these endeavors with cold cash and warm understanding.

David G. Cogan

David G. Cogan, M. D.

From an organizational point of view, the Laboratory has had a difficult year, suffering the loss of a substantial portion of its "permanent" staff and a threatened loss of the administrative autonomy with which the Laboratory has prospered these past forty-three years. The importance of this autonomy within the Harvard system cannot be over-emphasized.* It has been the strength of the Howe Laboratory in attracting basic scientists into a clinical environment and in permitting a measure of academic freedom in a predominantly service area. Its loss, or threatened loss, has meant the departure of our strong divisions of ophthalmic biochemistry and experimental histopathology.

Fortunately there are promising prospects for a successful reorganization. An Executive Committee has been formed to coordinate the Infirmary's research activities with those of the Howe Laboratory, and Dr. Grant has been appointed overall Ophthalmic Research Administrator for the Infirmary. We believe these are constructive steps and look forward to a continuation of the Laboratory's commitment to basic research and harmonious pursuit of clinical and academic goals. New staff is being recruited while those who are departing will continue their researches as an intact team at the National Eye Institute. We would like to think that the new ophthalmic laboratories at the National Institutes of Health are an extension of the Howe Laboratory.

Despite these disruptive events of organization, the year just past has been highly productive, and I am pleased to submit the following report of many and diverse activities and to acknowledge the great debt which we all feel to those agencies and individuals who have generously supported our endeavors with money and understanding.

GLAUCOMA

As must be evident to readers of these Annual Reports, an exemplary model of collaboration has developed over the years between the clinical operation of the Glaucoma Consultation Service and basic research on glaucoma in the Howe Laboratory, both under the supervision of Dr. Grant. A pleasing and productive participation has developed with members of the Resident, Fellow and Visiting Staff aimed toward better identification of types of glaucoma and improvement in treatment.

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* President Pusey recently described Harvard as a ". . . confederation of semi-independent baronies, squirearchies, and small farms."

Cases of glaucoma associated with epithelial invasion of the anterior chamber have been analyzed comprehensively by Dr. Joseph Kim. The results of freezing the ciliary body as a means of treatment has been analyzed by Dr. Bellows on the basis of 52 patients in whom this method has been employed. He has found a modest but encouraging degree of success in reduction of the intraocular pressure with relatively few serious complications. Varying in different kinds of glaucoma, significant benefit has been observed in 74% of eyes with open-angle glaucoma and in 36% of eyes with neovascular glaucoma. Dr. Bellows has now modified the freezing instrument to operate at a lower temperature by shifting from carbon dioxide to nitrous oxide to determine whether or not this would be advantageous.

The rate of water movement through the excised cornea and sclera has been measured by Dr. Bellows utilizing a specially constructed chamber and several different substances which have a strong avidity for water and might be applied to withdraw water from glaucomatous eyes under special circumstances.

There is need for clinically practical and easy means for measuring episcleral venous pressure in occasional patients who are suspected of having vascular abnormalities related to their glaucoma. To this end Dr. Bellows is testing a number of film-forming plastics that might be clinically applicable.

To improve means for measurement of rate of flow of aqueous humor in the eye, Dr. Murray Johnstone has been experimenting with dyes that react with albumin and thereby become fluorescent. The albumin in the aqueous humor of rabbits can be labelled in this way, and its change in concentration as the aqueous humor flows out of the eye can be measured fluorometrically, but difficulty has arisen in getting sufficient dye into the intact eye. Vasoflavin and a related dye have been found to have the desired reactive and fluorescent characteristics but penetrate the eye poorly either from local application or from systemic injection. To get workable levels in the aqueous humor requires injection of very large doses intravenously, raising considerations of toxic side effects.

Quantitative aqueous perfusion has been much used by Dr. Grant and other investigators in the Howe Laboratory for study of the aqueous outflow system of the eye. The findings that Dr. Grant has published have been the basis for much of the microsurgery now being performed on Schlemm's canal in various parts of the world. Studies by Dr. Bruce Ellingsen described in last year's Annual Report added much to understanding of the influence of trabecular meshwork and the walls of Schlemm's canal on aqueous outflow and helped in elucidating the mechanisms by which surgery on both inner and outer walls of Schlemm's canal have succeeded in reducing intraocular pressure in glaucomatous patients. The concepts that have grown out of this work were discussed this fall by Dr. Grant in a Symposium on Microsurgery of the Outflow Channels with leading investigators from England, Germany, Russia and the United States.

Now the quantitative aqueous perfusion procedure for study of the aqueous outflow system has been further refined and improved by Dr. Johnstone employing a means which permits measurements on isolated segments of the outflow system. This offers significant advantages over previous procedures which required a whole eye for measurement. With the new technique, the number of studies that can be made per eye is multiplied. This is important because of difficulties in obtaining adequate numbers of normal and glaucomatous human eyes post mortem. Perhaps more importantly, the new procedure utilizing excised segments of the aqueous outflow system provides more direct and convenient access for micromanipulation and dissection of the aqueous outflow channels than is feasible when working with a whole eye with relatively difficult access to the inner aspects of the outflow system. Now with higher microscopic magnification it should be possible to define the areas of dissection or manipulation more precisely than ever possible before. Initial observations utilizing the new technique have shown fundamental agreement with the findings of previous procedures concerning anatomic distribution of resistance to aqueous outflow and effects of trabeculotomy and trabeculectomy.

The whole subject of research on glaucoma and its governmental support is under review by a "Task Force" which has been appointed by Dr. Carl Kupfer of the National Eye Institute and includes Dr. Grant. One of the many points brought out in the course of discussions by this group was the fact that although 2% of the population may have intraocular pressure that is considered abnormally high and potentially damaging, only a fraction of those with abnormal pressure go on to lose part of their vision, and a still smaller fraction actually become blind. Since the ultimate objective of research on glaucoma is to prevent blindness, it seemed that special attention should be given to those particular forms of glaucoma and related conditions which have most commonly led to the greatest degree of visual loss. In line with these conclusions, Dr. Grant has instituted a retrospective analysis of the records of patients who have been reported legally blind from glaucoma, trying to determine specifically the types of glaucoma and the related conditions which have led to actual blindness.

A remarkable shallowing of the anterior chamber has been noted by Dr. Grant in a few cases to follow occlusion of the central retinal vein. Comparison has been made with contralateral unaffected eyes. The shallowing and narrowing of the angle has lasted for several weeks, but eventually, even without treatment, the depth has returned to normal. In one case, angle-closure glaucoma developed shortly after central vein occlusion, and iridectomy was performed. Anterior neovascularization and secondary glaucoma have subsequently developed in a small proportion of these cases.

Is there a neovascular or angiogenic factor in eyes with intraocular tumors? Such a factor, if found, might provide a clue to the mechanisms of development of new blood vessels on the iris and in the angle of the anterior chamber. Study along these lines has been a continuing interest of Drs. Walton, Bellows, Thoft and Grant. In conjunction with Dr. Judah Folkman at the Children's Hospital, an angiogenic factor has been found in the aqueous humor of an eye having both retinoblastoma and neovascular glaucoma, and in eyes with malignant melanomas and retinoblastomas before iris neovascularization, but has not yet been found in eyes having neovascular glaucoma secondary to diabetes or central retinal vascular occlusion. It is now being looked for in a large number of eyes having intraocular tumors without neovascularization of the anterior segment to determine whether this may offer a means for detection or identification of neoplasms in the eye, conceivably offering help in differentiating benign from malignant tumors and helping decide whether drastic treatment is needed or not.

Comparisons of the diagnostic merits of ordinary tonography and of tonography performed under cycloplegia, are being carried on by Dr. Grant, and Dr. Donaldson is continuing to accumulate fine serial stereophotographs of the optic nerveheads of patients under observation or treatment for glaucoma. These photographs are being made to obtain accurate year-by-year records of progressive changes that the optic nervehead undergoes. Dr. Chandler and Dr. Grant believe that an important indicator of the severity of the disease is provided by study of the changes in the optic nerves recorded in this way. While Dr. Donaldson's collection is growing for research purposes, it has become so evident that the photographic recording of the characteristics of the optic nervehead is a valuable adjunct to early detection of progression of damage that the Infirmary's photographic service under the supervision of Dr. Humphrey has undertaken to obtain photographs of the nerveheads of patients of the Glaucoma Consultation Service as part of the diagnostic and therapeutic routine.

Dr. Grant has further expanded his comprehensive cross-referenced information files on glaucoma covering the whole world's literature. This has repeatedly proven its value to those of the Infirmary who are interested in all sorts of clinical and experimental work on glaucoma.

The clinical information on aniridia and its associated glaucoma that has been accumulated by Drs. Grant and Chandler during many years is being meticulously analyzed by Dr. David Walton with more detailed and comprehensive clinical examinations and studies of the histopathology. He has already brought to light new features and new concepts of the condition, and it is to be hoped that eventually he may produce a definitive monograph on the subject, maybe in conjunction with Dr. Grant.

Dr. Paul Chandler's outstanding example of combining clinical investigation and innovation with clinical practice has been followed by Dr. Richard Simmons who has been regularly taking time to participate in activities of the Howe Laboratory and Glaucoma Consultation Service that are of mutual interest and benefit, such as working with Dr. Johnstone in the laboratory and operating room, and examining clinical aspects of treatment of certain forms of glaucoma by the microsurgical procedure of trabeculotomy ab externo. Dr. Chandler and Dr. Simmons have been evaluating clinically the use of a scleral shell to tamponade filtration blebs immediately following surgery for glaucoma, and have been finding that the incidence of post-operative choroidal detachment and flat anterior chamber is reducible by this means. Drs. Chandler, Simmons and Grant have continued their conjoint clinical studies of malignant glaucoma.

BIOCHEMISTRY

Cataracts

Under Dr. Kinoshita's direction, the main thrust of biochemical research in the Howe Laboratory for the past several years has been cataracts. The ultimate discovery of the cause and prevention of cataracts will come through an understanding of the metabolic processes by which the lenses of the eye are normally kept transparent and by detection of the biochemical faults which result in the cloudiness that we call cataracts.

The type of cataract which has been most amenable to study is that produced by excessive sugars in the blood and therefore called sugar cataract. Its clinical manifestation is seen in the occasional diabetic cataracts of human beings and the infrequent galactosemic cataracts of infants. Their experimental counterparts in animals or in the test tube are the cataracts produced by glucose, galactose, or xylose. It turns out that a common mechanism underlies all sugar cataracts. This involves the chemical reduction of the sugars to an alcohol form which is then trapped within the lens fibers and exerts an osmotic disequilibrium that in turn destroys the pump action necessary for the viability and clarity of the fibers. It further turns out that, according to the collaborative research of Dr. Ken Gabbay, a similar mechanism underlies the neuropathy and possibly other complications of diabetes.

Since it is not always possible to control sugar levels adequately under clinical circumstances, a vigorous search has been made these past few years for a means of preventing the chemical reduction of sugars into the osmotically active alcohol form. With the help of Ayerst Laboratory, a large number of compounds have been screened and synthesized. As noted in last year's Report, tetramethylene glutaric acid (TMG) gave promising results in preventing cataracts in the test tube but this agent was not effective in the intact animal because it was strongly bound to the serum proteins and did not get into the eye. A new compound, coded as Ayerst #284, has now been found to be considerably more potent than TMG and unlike TMG to have an inhibitory effect on galactose cataract formation in animals. The protective effect of this new compound is demonstrated by adding it to the diet along with the excessive sugar. However, the protection is incomplete and both Dr. Kinoshita and the Ayerst Laboratory are cautious in proposing this as a therapeutic agent while they search further for still more effective agents.

Eventually it is hoped to obtain a similar understanding of other types of cataract. At the moment very little is known about the underlying fault in the common "cataract of old age". Preliminary evidence suggests a defect in the pump mechanism. Normally this mechanism maintains appropriate concentrations of potassium and sodium within the lens but it is not known at present whether its failure is the cause or the result of the abnormality leading to cataracts of old age. The problem from an experimental point of view in studying senile cataracts is that there is no laboratory animal model which lends itself easily to reproduce the clinical conditions. The situation with congenital cataracts is different for we do have a strain of mice, imported from Japan, which do regularly develop cataracts, as do certain human babies, a few weeks after birth. These were illustrated in last year's Report where it was noted that Dr. Iwata and Mr. Christiansen had shown an initial fault in the ability of the lenses to maintain the sodium-potassium pump. These studies have been continued by Mr. Merola, Dr. Kabasawa and Dr. Obazawa with discovery of a primary deficiency in the enzyme, Na-K ATPase, which is a part of the pump mechanism. It has been found that this is an exclusive deficiency of the lens and that other tissues of the affected mice have a normal content of this enzyme.

While the foregoing studies have focussed principally on excessive sugars and defective pump mechanisms in the lens, Dr. Chylack has been concerned with cataracts that result from too little sugar and with the manner in which this involves the enzyme, hexokinase. Preliminary results indicate that this enzyme which is responsible for initiating the metabolic break-down of glucose is critically dependent on adequate concentration of glucose in the environment. This is a promising area in which to link basic biochemistry to a problem of clinical significance.

Aging of the human lens is accompanied by an increased scattering of the incident light, a phenomenon known to physicians as senile sclerosis and apparent to patients as a bothersome glare. When severe, the lens becomes opaque to constitute one of the more common forms of senile cataract. Believing that the increasing scattering of light depends, in turn, on the progressive aggregation of protein molecules in the lens, Drs. Jedziniak and Kinoshita have focussed their attention on measurement of the molecular size of the aggregates and on determination of the factors responsible for the aggregation. In conjunction with Prof. George Benedek (Physics Department, M.I.T.) they are studying the optical effects of these biochemical alterations. The aggregates have been found to have a molecular weight in the range of 100–500 million. Moreover, calcium ions which are present in high concentration in cataractous lenses can induce the aggregation, and calcium chelating agents such as EDTA can reverse the aggregation. The findings thus suggest that calcium plays a key role in the aggregation of lens proteins which occurs with normal aging and in some forms of senile cataract.

Retina

The enzyme glutamine synthetase is of especial interest to ophthalmic biochemists because it is present in higher concentration in the retina than in any other tissue. To obtain data on its role in the development of the retina, Dr. Reif-Lehrer studied its appearance in human embryos or fetuses obtained at the time of abortion or miscarriages or of neonatal death. She found very low activity at 35 weeks of development but almost adult levels of activity at 1–2 days after birth of a full-term infant.

Cells derived from a retinoblastoma and kept in continuous culture for two years were found to have no glutamine synthetase activity but activity could be induced in these malignant cells using cortisol under the appropriate culture conditions. Thus a presumably lost but normal function of these cells could be restored, giving evidence that de-differentiation of malignant cells can be reversed.

Studies in the chick embryo retina which attempt to pin-point the biochemical signals responsible for eliciting a given biochemical response have shown previously that certain glucocorticoids play a role in the appearance of glutamine synthetase activity. Dr. Reif-Lehrer has recently found that the antibiotic Actinomycin-D, which inhibits macromolecular synthesis, actually enhances the cortisol induction of glutamine synthetase. This provides us with information about the mechanism by which the concentration of this and probably other enzymes are controlled in the retina.

Another study in progress concerns the question "Is a given cell biochemically independent, or can some biochemical functions only be carried out by organized groups of cells?" Dr. Reif-Lehrer has obtained evidence which indicates, in contrast to previously published studies on this system, that single competent retinal cell may be capable of synthesizing glutamine synthetase outside of organized retinal structure. Such information may be pertinent to conditions such as wounds, where the normal tissue organization is disrupted.

Recently excitement in biochemical circles has been aroused by the discovery that the hormone Cyclic 3′5′ Adenosine Monophosphate (Cyclic AMP) has been found to mediate many intracellular processes which respond to external stimuli. The interest of ophthalmic biochemists has been especially aroused by the possibility that this cyclic AMP is an intermediate in the photoreceptors which converts the initial light stimulus into an electrical response that is ultimately relayed to the brain. In the Howe Laboratory Dr. Chader and several medical students are studying the properties of the adenylate cyclase which forms the cyclic nucleotide in the retina, and the enzyme phosphodiesterase, which destroys the cyclic AMP once its usefulness has been served. In this way the dynamic changes in cyclic AMP concentration can be ascertained under differing conditions of brightness, external stimulation by neurotransmitter substances, etc.

Besides cyclic AMP, it appears that cyclic guanosine monophosphate (cyclic GMP), a compound similar in structure to the cyclic AMP, may be important to retinal function or metabolism. The retina has an extremely active system for the synthesis and degradation of this compound which in several respects appears to be more active and more specific than its adenyl counterpart.

Since this is such a relatively new area of investigation, the function of cyclic nucleotides and of the enzymes which control their concentrations is not clear at present. These compounds are, however, in higher concentration in the retina than any other tissue of the body and it is expected that gaining an understanding of the role played by the cyclic nucleotides in the retina will be a big step in understanding the visual process.

Cornea

The role of soluble proteins in the rejection of corneal transplants is under study by Dr. Holt. The biochemistry of these proteins has been investigated surprisingly little. Approximately twenty soluble proteins have been identified, some of which are serum proteins and some are corneal glycoproteins (sugar-containing). To determine if one or more may induce immunologic rejection, a series of transplants are being performed in rabbits previously sensitized with the protein fractions. A later phase will entail determination of immunological sensitivity of patients who have suffered corneal rejection.

HISTOPATHOLOGY AND ELECTRON MICROSCOPY

The pioneering studies on ocular tissues for which Dr. Kuwabara is famous seem to increase in number and diversity with each year. His laboratory, small as it is, has been a mecca for all seeking help or paying homage to one of ophthalmology's foremost electron microscopists and experimental pathologists. Several of this past year's contributions may be mentioned.

A corneal abnormality occurring in families and bearing the awkward name of "posterior polymorphous dystrophy" has shown a surprising finding of epithelium rather than endothelium on the posterior corneal surface. A specimen obtained by Dr. Arthur Boruchoff at the time of corneal transplantation and studied by Dr. Kuwabara showed cells having the keratin fibrils and other morphologic features of typical epithelium even though the eye had never been either injured or had prior surgery that might have allowed ingrowth of epithelium.

Development of Descemet's membrane and the pathologic consequences of its rupture were subjects of study by Drs. Cogan and Kuwabara. They have observed that the successive laminae which constitute this membrane are being continuously laid down by the corneal endothelium throughout life and that irregularity of its contours, as from rupture, may result in excessive overgrowth of the membrane.

The biologic effects of laser photocoagulation have important bearing on the current treatment of diabetic retinopathy. The new argon photocoagulator has the theoretical advantage of destroying aberrant retinal vessels selectively. To determine just what these effects are at the tissue level, Dr. Okisaka, working under the guidance of Dr. Kuwabara at the Howe Laboratory and in conjunction with Drs. George Cahill and Lloyd Aiello at the Joslin Clinic, has exposed monkey eyes to the same amount of photocoagulation as is used in the treatment of human eyes. Observations were then made at appropriate time intervals by ophthalmoscopy, fluoroangiography and eventually by histology (including flat mounts) and electron microscopy. The degree of vascular damage was found to be considerably less than that of the neural tissue.

Continuing a long-time interest in the pathology and pathogenesis of diabetic retinopathy, Dr. Cogan analyzed some of the previously unemphasized aspects of this condition. Specifically, material was extracted and analyzed from the files which he and Dr. Kuwabara had collected, showing: the life cycle of diabetic microaneurysms; the initial disappearance of the intramural pericytes; the bulging of the wall with secondary proliferation of endothelium; the successive deposition of new basement membrane with ultimate occlusion of the microaneurysm, the hyalinization and lipidization of this thickened wall; and the final bursting (implosion) of the microaneurysms. Also studied were flat mounts of the choriocapillaris, where, in contrast to the diabetic vessels of the retina, minimal abnormalities could be found attributable to diabetes. Attempts were made to account for the characteristic central position of diabetic retinopathy on the basis of the differing hydrodynamic and morphologic architecture in the central and peripheral retina.

The ciliary zonules are classically represented as suspensory filaments that hold the lens in place. Their anatomic and biochemical nature has now been documented by Dr. Raviola's studies begun at the University of Pavia and completed in the Howe Laboratory. The zonules have been found by electron microscopy to consist of bundles or sheets of tubular fibrils, 110 to 120 Angstrom in diameter. When closely packed, they display a transverse banding with an average periodicity of 490 Angstrom. They are digested by alpha chymotrypsin and elastase but are not affected by collagenase. In other words, they resemble the microfibrils of elastic fibers.

At their origin in the ciliary body, the zonular fibers pursue a long course beneath the internal limiting membrane and within the intercellular spaces of the non-pigmented epithelium. At their insertion on the lens, the zonular fibrils fuse with the lens capsule. In the human lens, the fibrils penetrate more deeply in the capsule than in those of cows or monkeys, and approach the epithelial layer. This species difference seems undoubtedly related to the greater accommodative range of the human eye.

Dr. Kuwabara's studies on retinal damage by excessive amounts of light have been described in previous Annual Reports. Experiments of the past year have emphasized threshold levels of illumination for histologic damage. At these levels the photoreceptors become larger, irregular and shed an increased number of photoreceptor tips into the pigment epithelium. Yet they do not degenerate. Subthreshold levels of illumination appear to have a stimulant effect on the retinal cell activity.

Retinas of rats made deficient in vitamin A have been studied by Dr. Kuwabara in conjunction with Dr. Paul Newberne of the Nutrition Department at M.I.T. Although the experimental animals showed severe vitamin deficiency in other organs, the retinas were histologically normal. This was surprising in view of the degeneration reported by other investigators. One wonders if the discrepancy is due to varying levels of illumination and experiments are now in progress to check this out.

NEURO-OPHTHALMOLOGY

Circumstances, and personal interests, rather than logic or design, have centered neuro-ophthalmic activities in the Howe Laboratory. Here clinical and laboratory approaches to patients' problems have developed into a specialty within a specialty and found common cause with the departments of Neurology and Neurosurgery at the Massachusetts General Hospital.

Clinical studies of the past year have shown a genetic origin for many cases of ocular motor apraxia (Dr. Cogan) and have probed the pathologic basis for opsoclonus (Dr. Bienfang) and the visual loss in dysthyroid exophthalmos (Mr. Gittinger). A provocative and instructive session on neuro-ophthalmology was organized by Dr. Cogan for the Fall meeting of the Association of Research in Vision and Ophthalmology. Ten authorities presented what each considered the most missed diagnoses.

Experimental neuro-immunological studies in animals by Dr. Wray have suggested that circulating, sensitized lymphocytes in the blood may play an important role in the destruction of myelin in the optic nerve, brain, and spinal cord in patients with multiple sclerosis. It is now possible to measure the index of sensitivity of lymph node lymphocytes from animals with an induced demyelinating disease by an in vitro cell culture technique. This technique is being extended to detection of myelin-sensitized lymphocytes in the blood of multiple sclerosis patients both during and after recovery from an attack of this disease.

The aim of much of our electrophysiologic testing has been to separate rod and cone functions. Dr. Fricker finds his Synchronous Detector System accomplishes this well. The conventional wave forms of small electrical signals produced by the retina have been compared with those of the Synchronous Detector and found to yield similarly useful data on patients. Comparisons have been made utilizing visually evoked occipital potentials and have shown that the Synchronous Detector offers advantages in the presence of opaque ocular media. It has been established that the frequency of stimulation is an important parameter, and this implies that the Synchronous Detector method tests the subject in a manner which is not completely duplicated by tests based on the Average Waveform.

Eye movements are being recorded electronically and analyzed by Dr. Fricker and Mr. Sanders utilizing an optical pick-up device and modern methods of statistical processing data. The relative average time differences for motion of the two eyes has emerged as an interesting parameter measured in units of milliseconds. The velocities and acceleration for horizontal motion, under varying conditions, are now displayed instantly for both eyes. The system is being used to test patients with strabismus or neurologic disease and to compare these with normal persons.

An invitation from the Editor of the Handbook of Clinical Neurology prompted Dr. Cogan to review and analyze tumors of the optic nerve. The gliomas affect predominantly children and cause blindness in one, and occasionally in both, eyes. They are not known to be malignant in the sense of spreading elsewhere in the body but they may cause severe complications and sometimes death by extension into the brain. Meningiomas of the optic nerve are similar to those of the rest of the nervous system but are notable for their early recognition. Less common tumors of the optic nerve are hemangiomas, melanocytomas, congenital tumors, lymphomas, metastatic carcinomas, and tumors arising within the eye or adjacent structures.

Video recording (or taped television) has greatly facilitated the documentation of neuro-ophthalmic abnormalities. Drs. Cogan, Wray and Bienfang are "taping" cases that will eventually provide a valuable library for study and teaching. The first of what may develop into a series of tapes was prepared this past year for Video Digest on the subject of Internuclear Ophthalmoplegia. It is planned to prepare others for local use as time and material permits.

INSTRUMENTATION

Developing new apparatus and refining old has been a major preoccupation of Dr. Donaldson over the years. His instrument for measuring the depth of the anterior chamber has now been refined to a simple device for use with the Haag-Streit slit-lamp. Preliminary studies with it have indicated a diurnal variation of the depth of the chamber in some individuals.

The slit-lamp camera previously devised by Dr. Donaldson to give depth of focus not possible with conventional slit-lamp photography has now been modified with a diaphragm so that focussing can be done with a wide aperture but with instantaneous and automatic closure when the picture is taken. A further new feature is the use of a special prism assembly so that high power retro-illumination photographs can be made of lens opacities silhouetted against the red reflex of the fundus. This is the first time that three dimensional photographs of silhouetted cataracts have been made against the fundus reflex.

TOXICOLOGY

A second and much expanded edition of Dr. Grant's Ophthalmic Toxicology has been prepared and is expected to be available in 1972. This, together with the necessary review of the literature and an extensive correspondence (with physicians, lawyers, police departments, government agencies, laymen, and even with a Grand Jury) have comprised the toxicologic activity of the past year.

TEACHING

Teaching and the attendant learning process is an indissociable part of research and has been a long time function of the entire Howe Laboratory staff. It has at times been: formal, as in postgraduate courses, here and nationwide; less formal, as in the elective undergraduate courses for prospective ophthalmologists and in multiple seminars; and oftentimes totally informal as in the daily luncheon conferences or even coffee breaks in the Laboratory where the staff and visitors (Dr. Chandler is a "regular") find common interests. Taking time to communicate and to listen is essential to the type of clinico-laboratory correlation which the Howe Laboratory aims to achieve.

Some teaching sessions are perhaps especially noteworthy. Dr. Wray conducts a weekly conference for Residents and others who might be interested in neuro-ophthalmology. In recent years she and

Dr. Cogan have also given an intensive course in which approximately 100 ophthalmologists, neurologists, and neurosurgeons gather for a full week of didactic instruction. Dr. Grant holds a weekly glaucoma session with the Residents and interested physicians for leisurely discussion of questions that have arisen during the daily rush of clinical work. In addition he, together with Drs. Cogan and Kuwabara have maintained "hot-line" availability for discussion of specific problems, which in this past year have been heavily concerned with glaucoma, neuro-ophthalmology, pathology, and administration. The teaching accomplishments of Dr. Kinoshita have been no less noteworthy. In addition to heavy participation in formal courses, he has attracted students and residents for in-depth experience in research in ophthalmic biochemistry, to the physical limits of his laboratory.

The third in a series of Atlases of External Diseases was completed by Dr. Donaldson. This covers the Cornea and Sclera and is, by far, the most extensive of the series. Of the 400 or so illustrations, more than 100 are three dimensional and in full color. The text consists of abstracts of the cases along with a general discussion of the disease entities.

A brief text with 100 photographs illustrating ocular fundi in systemic disease was prepared by Drs. Cogan and Donaldson for the MEDCOM teaching series.

It seems fair to say that the teaching activities by the Laboratory staff have been abundant and diverse.

ORGANIZATIONAL AFFAIRS

The year 1971 was, if not the most critical, the most unsettling in the history of the Laboratory. It began with an organizational void left by Dr. Reinecke upon his departure for Albany in the previous year. The organization reached its all time low at the end of this year with the departure of Dr. Kuwabara and Dr. Kinoshita and their teams for Bethesda where they will establish comparable laboratories in the new National Eye Institute. Those of us who have remained have, needless to say, been most disconsolate.

How could such come about, we asked ourselves, when the

Laboratory was at the peak of its productivity, its interpersonnel morale at an all time high, its relationship with the outside community most pleasantly cordial, and the expectation of expanded space reaching concrete (literally) proportion? The manifold reasons certainly must include the uncertainties contingent on the retirement of the present Director within the next two years, the political atmosphere that is nationwide where basic research in a hospital environment is being challenged, and the opportunities being provided for research in a more favorable atmosphere elsewhere. Perhaps, we told ourselves, we had failed to represent adequately the continuity of the Laboratory's commitment to research; perhaps we had been too smugly confident that sound research was sufficient claim for survival; perhaps in emphasizing the physical needs of research we had failed to communicate the ideologic needs of the investigators.

Whatever the cause, something needed to be done and Drs. Grant and Cogan have spent vast time and thought in reorganization of the Laboratory's affairs. Dr. Grant has, in fact, taken on the matter as a research project itself, employing the same thoroughness in data collecting and control as has characterized his more scientific investigations. The Infirmary has wisely appointed him its Ophthalmic Research Administrator so that there may be effective coordination of the Infirmary with the Laboratory's operation. There is every promise for re-establishment of the Laboratory's stability despite the recent major losses in personnel.

Mr. Cecil Drinker has joined the Laboratory and will add great strength to the administrative functions in which we feel we have been lax. Dr. Henry Fukui joins the Laboratory to replace Dr. Jin Kinoshita as full time biochemist. Dr. Leo Chylack will also continue part time in his biochemical studies while serving as ophthalmologist to the Peter Bent Brigham Hospital. The electron microscopic laboratory which has been so preeminent under Dr. Kuwabara's direction is a matter of major concern in our reorganization, but we anticipate a firm decision in the near future. A full time head of this branch will probably be appointed by the time this Report is in print. We should also note that both Drs. Kinoshita and Kuwabara are requesting leaves of absence rather than resignations so that we look forward to continuation of assistance from them and, not impossibly, their eventual return if this seems propitious within the time limit of their leave.

Thus, although the year has been most disquieting, we are optimistic that the major organizational problems have now been solved and we will again be in full operation by the time we move into new quarters.

HONORS AND AWARDS

During the past year both Drs. Kinoshita and Kuwabara were made full academic professors at the Harvard Medical School. The Howe Laboratory is proud to have had four tenured professors on its staff.

At the Fall meeting of the American Academy of Ophthalmology and Otolaryngology, Dr. Cogan was a Guest of Honor of the Academy and Dr. Grant a participant in one of its major symposia.

Sharing the common weakness of deriving pleasure from approval, we read with satisfaction in the five year Progress Report of our sister institution, the Francis I. Proctor Foundation, the following historical note: "The Howe Laboratory was the model upon which Mrs. Proctor decided to pattern her Foundation. Its (the Howe Laboratory's) record of achievement was consistently excellent . . . ascribed . . . in part to the Laboratory's administrative autonomy within the University."

CONTRIBUTIONS

While project support involving large funds must necessarily provide the major resource for research, we are equally grateful for the many smaller contributions that we receive, not only because they provide the uncommitted funds so necessary to research, but because of the benevolent spirit in which they are given. As testimony to this appreciation we have usually cited in these Annual Reports a case or two which has particularly touched our sensitivities. In this tradition I cite this year the case of a patient with macular degeneration whom we have not been able to help but who continues to have faith in our efforts and who annually contributes to the Howe Laboratory in commemoration of her deceased mother's birthday. Is there any finer way to combine sentiment and service? I also cite the case of a regular benefactor whose employer matches his gift to the Laboratory. Thus through him we are doubly enriched.

We may also disclose, as this Report goes to press, that a sizeable estate, "in excess of $200,000", has been willed to the Laboratory by Mrs. Joan Moser. Mrs. Moser and her husband were tragically killed in an airplane accident while travelling abroad. Her gift if allowed by the Probate Court will be the largest gift of unrestricted funds (potentially endowment funds) which the Laboratory has received since its founding in 1927.

David G. Cogan, M.D.
Director

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For General Expenses

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Pressure regulating mechanisms in glaucoma
Research Career Development Award
Cataracts
Metabolism of the normal and abnormal ocular lens
Ultrastructure of retina and retinal disease
Studies of iris ultrastructure
Differentiation of chick retina
Studies on diabetic retinopathy

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Congenital anomalies of the retina. *Birth Defects: Original Article Series* Vol. VII, No. 3, March 1971. pp. 41–51.

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Ocular and cutaneous disorders, appendix A. *Dermatology in General Practice.* Ed. T. B. Fitzpatrick, N.Y., McGraw Hill, 1971. pp. 1991–1998.

Atlas of External Diseases of the Eye. Vol. III. Cornea and Sclera. St. Louis, Mosby, 1971. 475 pp.

Epstein, D. L.

Introduction to discussion of lens and red cell sulfydryl membrane groups. Exp. Eye Res. *11*:351–355, May 1971.

Fricker, S. J.

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Analysis of the visual evoked response by synchronous detector techniques. I. Patients with cataracts. Invest. Ophthalmol. *10*:340–347, May 1971.

Electrical responses of the visual system. Internat. Ophthalmol. Clin. *9*:851–1105, Winter 1969 (pub. 1971).

ERG and VER with the synchronous detector. Internat. Ophthalmol. Clin. *9*:935–969, Winter 1969 (pub. 1971).

The clinical significance of ERG time delay determination by means of a phase-sensitive detection system. 7th International Symposium on ERG, September 14–18, 1969, Istanbul, Turkey. Pub. 1971.

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Dynamic measurements of horizontal eye motion. I. Acceleration and velocity matrices. Invest. Ophthalmol. *10*:724–732, September 1971.

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Glutamine synthetase activity in human retinal tissue. Enzyme activity in the normal retina and cortisol induction in cultured cells derived from retinoblastoma. Arch. Ophthalmol. 86:72–76, July 1971.

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Actinomycin-D enhancement of glutamine synthetase activity in chick embryo retinas cultured in the presence of cortisol. J. Cell Biol. 51:303, October 1971.

with LaVail, M. M.: Glutamine synthetase in the normal and dystrophic mouse retina. J. Cell Biol. 51:303, October 1971.

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Wray, S. H.

with Pavan-Langston, D.: The reevaluation of edrophonium chloride (tensilon) tonography in the diagnosis of myasthenia gravis, with observations on some other defects of neuromuscular transmission. Neurology 21:586–593, June 1971.

LECTURES

Bienfang, D. C.

Introduction to neuro-ophthalmology. Series of monthly lectures, Third Year Class, Harvard Medical School, April–December 1971.

Gross anatomy and microscopic anatomy of the brain stem. Postgraduate Course in Neuro-ophthalmology, Harvard Medical School, April 13, 1971.

The oculomotor organization of the brainstem. Department of Ophthalmology, Albany Medical Center, in Albany, New York, October 7, 1971.

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A glucocorticoid hormone receptor in the chick embryo retina. Association for Research in Vision and Ophthalmology, in Sarasota, Florida, April 27, 1971.

Hormonal effects on the neural retina. Postgraduate Course in Ophthalmology, Harvard Medical School, September 1971.

Chylack, L. T., Jr.

with Michon, J.: Metabolic diseases and the eye. Postgraduate Course in Ophthalmology, Harvard Medical School, September 7, 1971.

Introduction to clinical ophthalmology. Series of lectures to Third and Fourth Year Class, Harvard Medical School, October–November 1971.

Cogan, D. G.

Clinical pathology. Lecture series. Elective Course, Harvard Medical School, January–February 1971.

Research on blinding eye disease. Lions Club, in Taunton, February 20, 1971.

Ocular fundus, Parts I and II. House Officer Lectures, Massachusetts General Hospital, Medical Staff, March 15 and 31, 1971.

Postgraduate Course in Neuro-ophthalmology. Lecture series. Harvard Medical School, April 12–17, 1971.

Growth and regenerative potential of Descemet's membrane. Irish Ophthalmological Society, in Dublin, Ireland, April 30, 1971.

Inborn errors of metabolism. North of England Ophthalmological Society, in Sheffield, England, May 15, 1971.

Chicago Ophthalmological Society, in Chicago, Illinois, May 22, 1971:

Some unemphasized aspects of diabetic retinochoroidopathy.
Ocular motor short circuits.

Lipid studies on eye tissue. Clinical Research Center, Massachusetts Institute of Technology, in Cambridge, June 8, 1971.

Missed diagnoses in neuro-ophthalmology. Neuro-ophthalmology Symposium, Association for Research in Vision and Ophthalmology, in Las Vegas, Nevada, September 18, 1971.

Heredity of congenital ocular motor apraxia. American Academy of Ophthalmology and Otolaryngology, in Las Vegas, Nevada, September 20–24, 1971.

Ophthalmic pathology. Series of lectures, Postgraduate Course in Ophthalmology, Harvard Medical School, November–December 1971.

DONALDSON, D. D.

Ocular injuries. Course in Industrial Ophthalmology, Harvard School of Public Health, January 19, 1971.

Oklahoma City Academy of Ophthalmology and Otolaryngology, University of Oklahoma Medical Center, in Oklahoma City, Oklahoma, March 19, 1971:
  External eye disease associated with some systemic diseases.
  Some unusual atrophic conditions of the iris.
  Conjunctival tumors.

Symposium on Diseases and Surgery of the Lens, Louisiana State University Medical Center, in New Orleans, Louisiana, April 2–3, 1971:
  Classification and morphology of cataracts.
  Etiology of cataracts, Parts I and II.
  Iatrogenic conditions.

Melanotic conditions of the conjunctiva. Dermatology Rounds, Massachusetts General Hospital, April 27, 1971.

Ocular manifestations of systemic disease. Ophthalmology for Internists, Pediatricians and General Practitioners. Department of Continuing Education, Harvard Medical School, May 7, 1971.

Diseases of the cornea. Postgraduate Course in Corneal Disease, Harvard Medical School, June 17–19, 1971.

External eye diseases. Lancaster Courses in Ophthalmology, in Waterville, Maine, August 23–26, 1971.

Postgraduate Course in Ophthalmology, Harvard Medical School: Neuro-ophthalmology, September 11–November 3, 1971.
  Orbital fractures, October 6, 1971.
  Diseases of the anterior segment, December 8–17, 1971.

New developments in photography. Ophthalmic Photographers Society, Inc., in Las Vegas, Nevada, September 19, 1971.

Lesions of the anterior chamber angle. Wills Eye Hospital, in Philadelphia, October 11, 1971.

External diseases and ocular photography. University of Pennsylvania Postgraduate Course, in Philadelphia, Pennsylvania, October 12–16, 1971.

St. Louis University School of Medicine, in St. Louis, Missouri, December 2–3, 1971:
  Technique of ocular stereophotography.
  Optical methods of recording eye disease.

Neuro-anatomy with special reference to neuro-ophthalmology. Series of lectures, Washington Hospital Center, in Washington, D.C., December 4, 1971.

House Officer Lectures, Massachusetts Eye and Ear Infirmary:
  Orbital fractures, February 17, 1971.
  Cataracts, Parts I and II, June 16 and 23, 1971.

FRICKER, S. J.

Electrophysiology in the diagnosis of pediatric ophthalmic problems. New England Ophthalmological Society, January 20, 1971.

Strabismus. Boston Visiting Nurses Association and Boston School Nurses, in Boston, April 7, 1971.

Electrophysiological measurements. Northeastern University, in Boston, April 26, 1971.

Symposium on medical therapy and its complications. Alumni Association of the Massachusetts Eye and Ear Infirmary, April 28, 1971.

Differential time delays and eye motion. New England Ophthalmological Society, April 29, 1971.

Drugs: The patient and his eyes. Ophthalmology for Internists, Pediatricians and General Practitioners, Harvard Medical School, May 7, 1971.

Optic nerve lesions and degenerative retinopathies. Third Year Class, Harvard Medical School, May 15, August 14 and October 30, 1971.

GRANT, W. M.

Glaucoma. Fourth Year Class, Harvard Medical School, February 16, 1971.

Corticosteroid glaucoma and ocular effects of mercury. Symposium on Medical Therapy and Complications. Alumni Association of the Massachusetts Eye and Ear Infirmary, April 28, 1971.

How to recognize glaucoma, signs and symptoms. Medical Staff Officer Lecture, Massachusetts General Hospital, April 23, 1971.

Postgraduate Course in Ophthalmology, Harvard Medical School:
  Tonography and tonometry, September 1, 1971.
  Toxicology of the eye, October 26, 1971.
  Glaucoma in infancy and childhood, November 22, 1971.

Symposium on microsurgery of the outflow channels. Laboratory research. American Academy of Ophthalmology and Otolaryngology, in Las Vegas, Nevada, September 21, 1971.

Glaucoma. Third Year Class, Harvard Medical School, October 8, 1971.

IMAIZUMI, M.

with Kuwabara, T.: Development of the rat iris. Association for Research in Vision and Ophthalmology, in Sarasota, Florida, April 26, 1971.

IWATA, S.

Mechanism of development of hereditary cataract in mice. Association for Research in Vision and Ophthalmology, in Sarasota, Florida, April 26, 1971.

Jedziniak, J. A.

Activators and inhibitors of lens aldose reductase. Association for Research in Vision and Ophthalmology, in Sarasota, Florida, April 26, 1971.

Johnstone, M. A.

Glaucoma. Postgraduate Course in Ophthalmic Nursing, Massachusetts Eye and Ear Infirmary, October 4, 1971.

Kinoshita, J. H.

Aldose reductase in cataracts. Association for Research in Vision and Ophthalmology, in Sarasota, Florida, April 26, 1971.

Series of lectures on eye biochemistry. Lancaster Courses in Ophthalmology, in Waterville, Maine, July 14–16, 1971.

Series of lectures on eye biochemistry. Postgraduate Course in Ophthalmology, Harvard Medical School, August 31–September 2, 1971.

Lens metabolism. Department of Ophthalmology, Juntendo University, in Tokyo, Japan, October 13, 1971.

Biochemical basis of cataract. Symposium on the Lens, in Hakone, Japan, October 17, 1971.

Kuwabara, T.

Scanning electron microscopy. House Officer Lecture, Massachusetts Eye and Ear Infirmary, February 2, 1971.

Anatomy and pathology of the eye. Series of lectures, Elective Course, Harvard Medical School, February 1971.

Scanning electron microscopy of soft tissue. New England Electron Microscopy Society, in Boston, March 26, 1971.

Pathology of the eye. Series of lectures, Department of Pathology, Massachusetts General Hospital, April 4 and 7, 1971.

Histology and electron microscopy of muscle. Postgraduate Course in Neuro-ophthalmology, Harvard Medical School, April 12, 1971.

Diabetic retinopathy. Joslin Research Laboratory, in Boston, May 18, 1971.

Posterior polymorphous degeneration: Its pathology. Cornea Symposium, Columbia University, in New York City, June 11, 1971.

Anatomy of the cornea. Postgraduate Course in Diseases of the Cornea, Harvard Medical School, June 17, 1971.

Anatomy and pathology of the eye. Series of lectures, Lancaster Courses in Ophthalmology, in Waterville, Maine, July 1971.

Retinal light damage by xenon lamp. Seminar at Xerox Corporation, in Rochester, New York, July 24, 1971.

Structure of cell surfaces. Electron Microscopy Society of America, in Boston, August 18, 1971.

Diabetic retinopathy. Jerusalem Symposium on Blindness, in Jerusalem, Israel, August 28, 1971.

Anatomy and pathology of the eye. Series of lectures, Postgraduate Course in Ophthalmology, Harvard Medical School, September 1–10 and November 16, 1971.

Development of the optic nerve. Second MacKenzie Memorial Symposium, in Glasgow, Scotland, September 8, 1971.

Anatomy and pathology of the eye. Wills Eye Institute, in Philadelphia, Pennsylvania, September 1971.

Light damage of the retina. Department of Ophthalmology, Tufts University School of Medicine, in Boston, October 5, 1971.

Pathology of the lens. Japan-United States Lens Symposium, in Hakone, Japan, October 16, 1971.

Pathology of corneal diseases. Juntendo University Medical School, in Tokyo, Japan, October 18, 1971.

Structure of the eye. Northeastern University, in Boston, October 1971.

Pathology of laser-treated retina. Tokyo Ophthalmology Society, in Tokyo, Japan, October 20, 1971.

Diabetic retinopathy and photocoagulation. Chubu Ophthalmology Society, in Tsu, Japan, October 24, 1971.

Histological studies in laser-treated retinas. New England Ophthalmological Society, November 17, 1971.

Retinal damage by subthreshold light exposure. Association for Research in Vision and Ophthalmology, in Las Vegas, Nevada, November 1971.

Okisaka, S.

with Kuwabara, T.: Histology of laser-treated retina. Association for Research in Vision and Ophthalmology, in Sarasota, Florida, April 29, 1971.

Reif-Lehrer, L.

with LaVail, M.: Development of glutamine synthetase activity in the normal and dystrophic mouse retina. Association for Research in Vision and Ophthalmology, in Sarasota, Florida, April 27, 1971.

Induction of glutamine synthetase in the chick embryo retina. Research Department, Retina Foundation, in Boston, August 25, 1971.

Regulatory mechanisms. Postgraduate Course in Ophthalmology, Harvard Medical School, September 9, 1971.

Snyder, C.

Medicine and literature. Ladies Visiting Committee, Massachusetts Eye and Ear Infirmary, January 20, 1971.

Now, let us take a look at the record. Miami Ophthalmological Society, in Miami, Florida, March 29, 1971.

Unwashed Willie. Ear, Nose, and Throat Clinical Conference, Massachusetts Eye and Ear Infirmary, June 16, 1971.

An introduction to the history of ophthalmology. Postgraduate Course in Ophthalmology, Harvard Medical School, September 2, 1971.

Wray, S. H.

Neuro-ophthalmology. Postgraduate Course in Neurology, Massachusetts General Hospital, March 8–19, 1971.

Postgraduate Course in Neuro-opthalmology. Lecture series. Harvard Medical School, April 12–16, 1971.

Migraine hallucinations in children. American Academy of Neurology, in New York, New York, April 28, 1971.

Postgraduate Course in Ophthalmology for Internists, General Practitioners and Pediatricians, Harvard Medical School:

The visual pathways and field defects, May 7, 1971.

Motor neuro-ophthalmology, May 8, 1971.

Tobacco amblyopia. Medical Staff, Mt. Auburn Hospital, in Cambridge, July 1, 1971.

Pseudotumor cerebri. Medical Staff, Massachusetts General Hospital, August 12, 1971.

Ocular motility disorders in brain stem gliomas. Medical Staff, Peter Bent Brigham and Children's Hospitals, September 29, 1971.

Postgraduate Course in Ophthalmology, Harvard Medical School:

Oculomuscular disease, October 22, 1971.

Supranuclear gaze palsy, October 25, 1971.

Internuclear ophthalmoplegia and nystagmus, November 1, 1971.

Oculomotor apraxia and case conference, November 3, 1971.

Visiting Professor to the Department of Neurosurgical Surgery, University of Chicago and Rush Medical School, University of Illinois, in Chicago, Illinois, November 17–20, 1971:

Ophthalmic signs in brain stem lesions.

Involuntary eye movements.

Abnormalities of the pupil.

Ocular myopathies.

Herpes zoster ophthalmicus. New England Ophthalmological Society, December 15, 1971.

EPILOGUE

Believing that, as Alan Gregg once remarked, research is people, and that, if we may add a corollary, a Laboratory is the instrument of those people, I would like to present a brief and personal account of four persons who have contributed immeasurably to making the Laboratory the instrument that it is. The occasion is their departure for Bethesda, Maryland, where together they will establish new and expanded laboratories at the National Institutes of Health for continuation of the researches which have distinguished them and the Howe Laboratory in ophthalmic research.

These Annual Reports have documented their specific and many contributions going back for nearly two decades. What has not been apparent are the elusive influences which directed them into research and eventually into research on the eye. Perhaps some inkling of these influences is apparent in the following sketches.

David G. Cogan M.D.

JIN KINOSHITA

Jin Kinoshita was a Junior College student in San Francisco at the time of Pearl Harbor. He and his family and thousands of other Japanese-Americans were moved to an improvised concentration camp at Santa Anita race track. For the next 10 months, the family home was a reconverted horse stall. Education was necessarily a hit-or-miss affair but the leadership qualities of the 18-year-old Kinoshita — and the quality for making the best of a bad situation — emerged in his organization of the Boy Scout troop in what must have been one of the world's finest parade grounds.

Thence to Utah where he was assigned farm work in the beet-growing fields and eventually to college on the East Coast (Bard College) under the benevolent auspices of the Friends Service Committee. For his Ph.D. degree in biochemistry, he came to Harvard as a result of one of those chance personal contacts that shape the lives of all of us. And another chance personal contact, fortunate for us, directed him to the Howe Laboratory.

What has all of this to do with the generation of one of the world's top investigators in ophthalmic research? Possibly very little, but we would attribute to it his characteristic understanding of, and empathy for, the many students and colleagues who have worked with him in the Laboratory. And it is to the feed-back of these associates to which he attributes his own motivations.

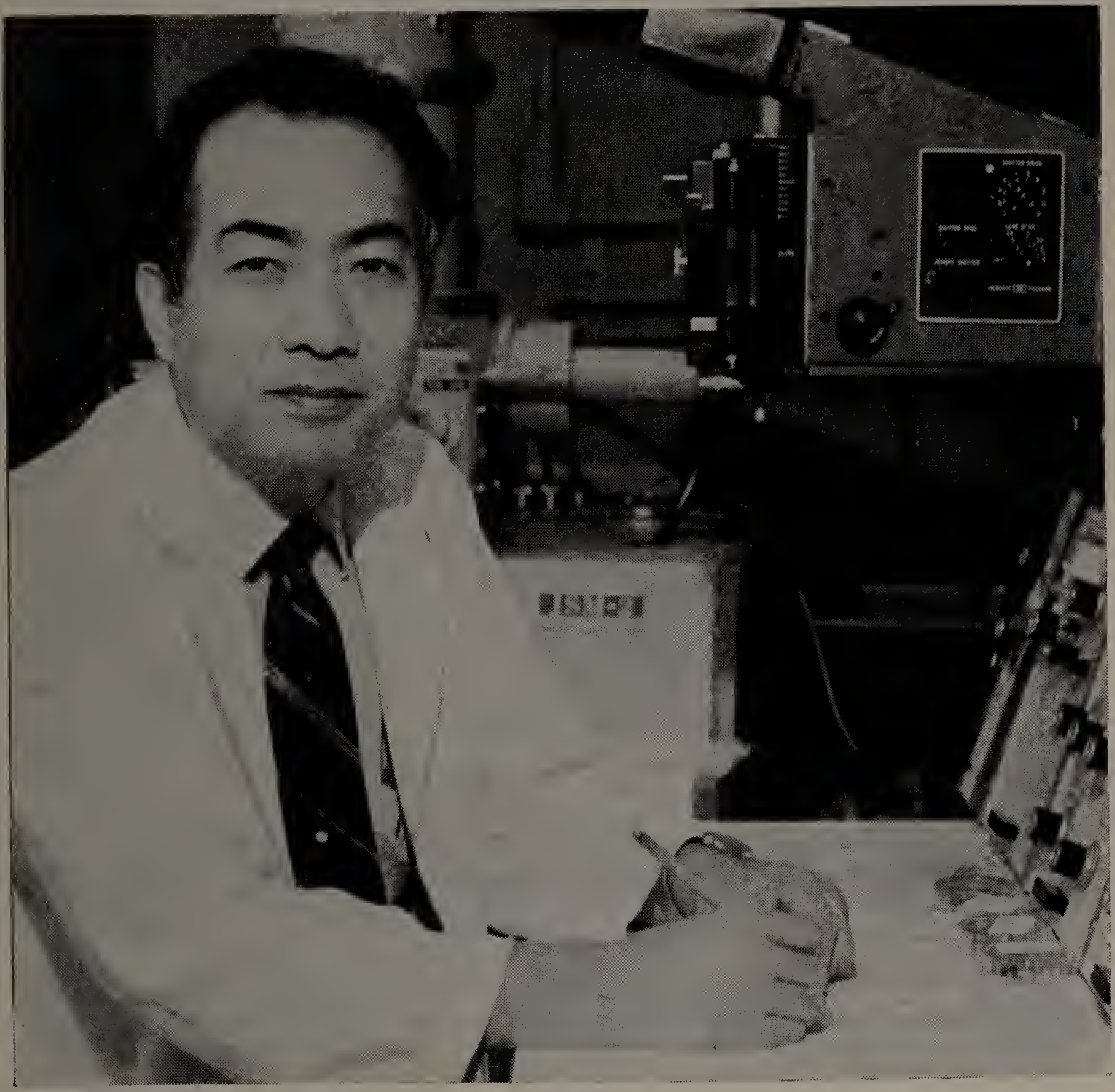
He now leaves to be Chief of the new Laboratory of Vision Research at the National Eye Institute. With him goes a bit of us as well.

TOICHIRO KUWABARA

The son of a prominent medical family in southern Japan, Toichiro Kuwabara decided to become a pathologist. He was in fact a member of the Pathology Department at the University of Fukuoka while some of us in the Howe Laboratory were studying fat formation in the cornea. We needed a pathologist, even more than we realized, and had obtained a modest source of support for the fat studies. Dr. Kuwabara had already distinguished himself in Japan as an unusually gifted investigator. It was our good fortune to attract him to the Howe Laboratory, at first for a year and later as a permanent and prominent member of the Staff.

Suddenly things began to happen. The fat studies led to applications far beyond the eye. They also took unexpected turns (a phenomenon of creative research!) and led to the discovery of a totally new way of preparing and studying the retinal blood vessels and their diseases. The histochemistry of the retina and the interrelationships of the neurones and glia were elucidated by new and revealing techniques. And, finally, electron microscopy of the eye was pioneered in the Howe Laboratory. All of these, and many other accomplishments, are attributable to the creative genius and meticulous industry of Dr. Kuwabara.

What is the formula for such a productive person? Surely much of it must be genetic. We suspect much is also due to rigorous self-discipline. We would like to believe a favorable environment has played a role. But whatever the secrets are, Dr. Kuwabara has generously reflected glory on all of us for his distinction in ophthalmic research. He now leaves to be Head of the Section on Experimental Pathology, at the National Eye Institute where he will establish its first laboratory of experimental pathology.



GERALD CHADER

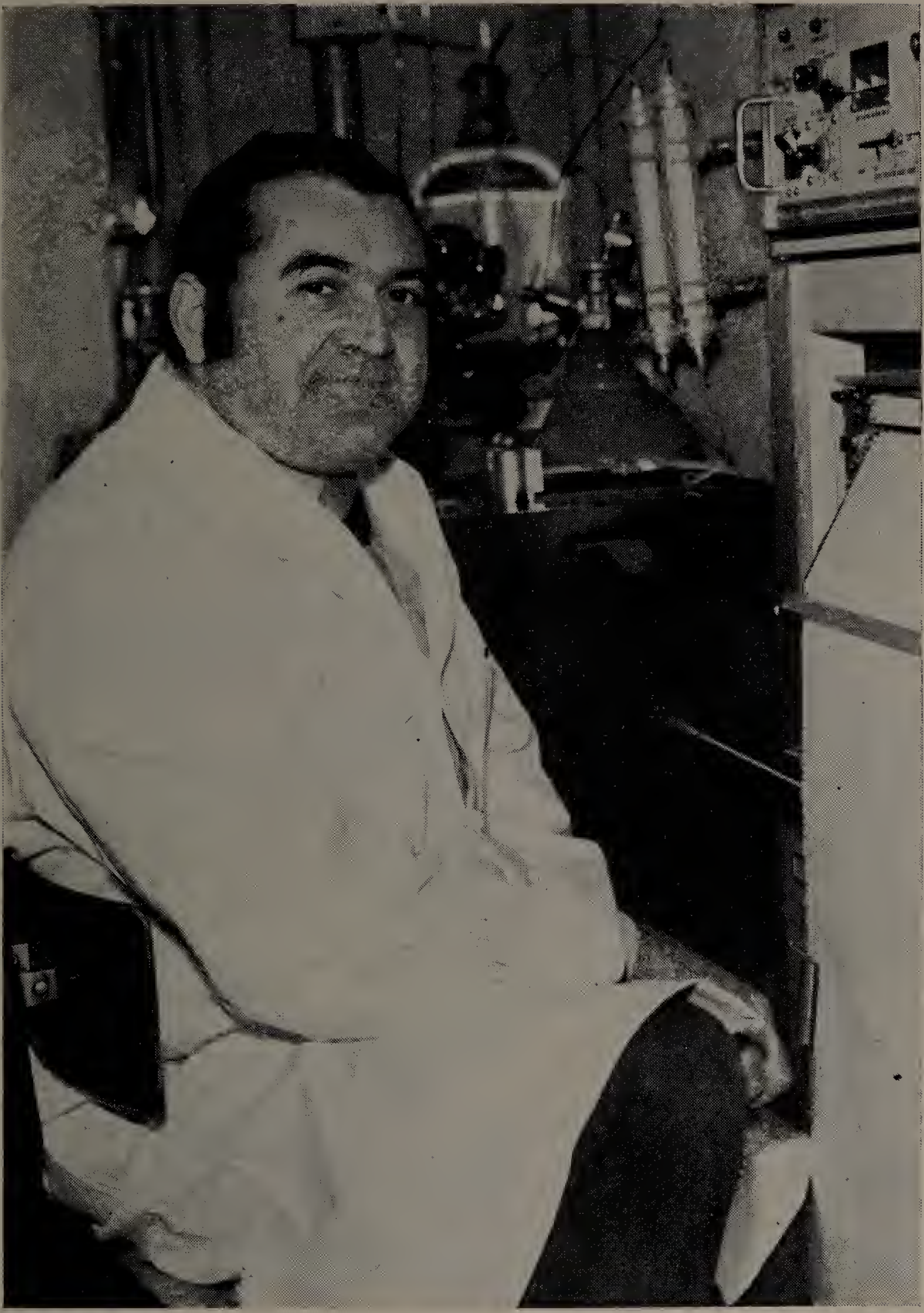
Jerry aimed to be a history teacher during his collegiate days but the teacher-demand was for science and he had majored in chemistry. Thus on graduation he became a chemistry teacher, in a Buffalo high school. But then came the draft and as a draftee he was assigned to studies on stress, specifically on cortisol metabolism, at the Fort Knox laboratories. This first-hand introduction into biochemistry and the challenges of applying biochemical knowledge to clinical problems determined his subsequent career. More specifically, when his director of research at Fort Knox left for the University of Kentucky, so did Jerry, there to obtain a Ph.D. degree and spend a post-doctoral year.

Transferring later to the Department of Biochemistry at Harvard, he was continuing his studies on cortisol while Dr. Reif-Lehrer was studying control mechanisms in the retina. A chance seminar suddenly revealed their common interests and Dr. Chader joined the Howe Laboratory. This was in 1969. Thus Jerry has been with us but a short time — we wish it might have been much longer — but he is already a recognized investigator in ophthalmic research and an inspiring teacher of many students. He will be Research Chemist at the National Eye Institute and continue his collaboration with Dr. Kinoshita and Dr. Kuwabara.

LORENZO MEROLA

Larry Merola arrived in the Laboratory in 1955 by a circuitous route. It all began, he believes, with a toy chemistry set given to him as a child. The fascination with test tubes and colored solutions stayed with him later as a high-school student in Worcester and still later as a pre-medical student at Holy Cross. The chance assignment of a student project in photosynthesis consolidated his interest in biochemistry, for the then infant science of chromatography was opening up new and exciting possibilities for identification of various carbohydrates.

Financial need directed him into industry after graduation, first as an analytic chemist in the steel industry and later as an investigator of tobacco leaf aging for a cigarette company. But then a postgraduate year at Boston University put him in contact with a professor who had had contact with the Howe Laboratory. Thus Larry heard of us and we of him with the result that he joined the Laboratory. For 16 years he has been one of Dr. Kinoshita's most valuable assistants and a major asset in the Laboratory's manifold operations.



FORM OF BEQUEST

The Howe Laboratory of Ophthalmology is an independent department of the Harvard Medical School and is jointly supported by a restricted endowment of Harvard University and by the Massachusetts Eye and Ear Infirmary.

For the information of those who may wish to contribute to this Laboratory, a form of bequest is here set forth:

I GIVE AND BEQUEATH TO THE HOWE LABORATORY OF

OPHTHALMOLOGY .... DOLLARS

TO BE APPLIED TO THE USES OF SAID LABORATORY.

Such bequests are managed by the Treasurer's Office of Harvard University and are tax deductible. The income is accredited to the Laboratory.

Secretarial and Technical Personnel

Barbara J. Beckman, Roberta F. Beer, Inez M. Berry, Russell A. Carlson, Jacalyn Coghlin, Jack Cummins, Beth S. Davis, Robert M. DePaolo, Dorothy A. Drago, Lancelot F. Drummond, Susan C. Flanders, Edward M. Gadowski, Marsha E. Goldman, Carole A. Hardy, Barbara L. Harper, Barbara H. Herndon, Max T. Irwin, Edith S. James, Kerstin G. Kobel, Roger C. Lancaster, Agnes Love, John W. McCready, Audrey C. Melanson, Werner Mueller, Jr., Rasma Niedra, E. Joann Perkins, Charles O. Rogers, Maria D. Ryerson, James J. Sanders III, Laura R. Saunders, Marjorie E. Saunders, Richard T. Sullivan, Malcolm W. Swan, Bill Tung, May W. Vuilleumier, Olga Wehm-Dalton, Deborah Winn, Marcia Winn, Ellen M. Yates.